A ZFN/piggyBac step closer to autologous liver cell therapy.

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Authors: A N Mattis, H Willenbring

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Public Summary:
This publication represents a review and commentary on a recent article in the journal Nature, by Yusa et al. titled "Targeted gene correction of a1-antitrypsin deficiency in induced pluripotent stem cells," published in the October 2011 issue. The scientific abstract represents a direct quotation of that article. In the Nature article, Yusa et al. were able to use a cell culture method called homologous recombination to repair a genetic defect in the disease alpha-1-antitrypsin. In the alpha-1-antitryspin disease, the gene is mutated so that when the encoded protein becomes produced, the final protein product is defective. This protein that is normally secreted by the liver to protect the lungs, becomes trapped within liver cells. The end result is damage to both the lungs as well as the liver. The lungs go on to develop emphysema while the liver eventually develops cirrhosis. Unlike previous genetic repair technology, after repair of the defective gene, this method was able to leave the cell chromosomes without significant remaining foreign DNA. When this technology is combined with patient-derived stem cells called induced pluripotent stem cells (iPSCs), it presents an opportunity to correct faulty genes within a tissue culture system. The authors were able to also show that transforming the IPSCs into liver cells also showed a functional correction within liver cells. This method represents a next step in genetic correction technology.

Scientific Abstract:
Human induced pluripotent stem cells (iPSCs) represent a unique opportunity for regenerative medicine because they offer the prospect of generating unlimited quantities of cells for autologous transplantation, with potential application in treatments for a broad range of disorders. However, the use of human iPSCs in the context of genetically inherited human disease will require the correction of disease-causing mutations in a manner that is fully compatible with clinical applications. The methods currently available, such as homologous recombination, lack the necessary efficiency and also leave residual sequences in the targeted genome. Therefore, the development of new approaches to edit the mammalian genome is a prerequisite to delivering the clinical promise of human iPSCs. Here we show that a combination of zinc finger nucleases (ZFNs) and piggyBac technology in human iPSCs can achieve biallelic correction of a point mutation (Glu342Lys) in the alpha(1) -antitrypsin (A1AT, also known as SERPINA1) gene that is responsible for alpha(1) -antitrypsin deficiency. Genetic correction of human iPSCs restored the structure and function of A1AT in subsequently derived liver cells in vitro and in vivo. This approach is significantly more efficient than any other gene-targeting technology that is currently available and crucially prevents contamination of the host genome with residual non-human sequences. Our results provide the first proof of principle, to our knowledge, for the potential of combining human iPSCs with genetic correction to generate clinically relevant cells for autologous cell-based therapies. (HEPATOLOGY 2012.).